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# ARYLBORONIC ACID-MEDIATED GLYCOSYLATION OF 1,2-DIHYDROXYGLUCOSES

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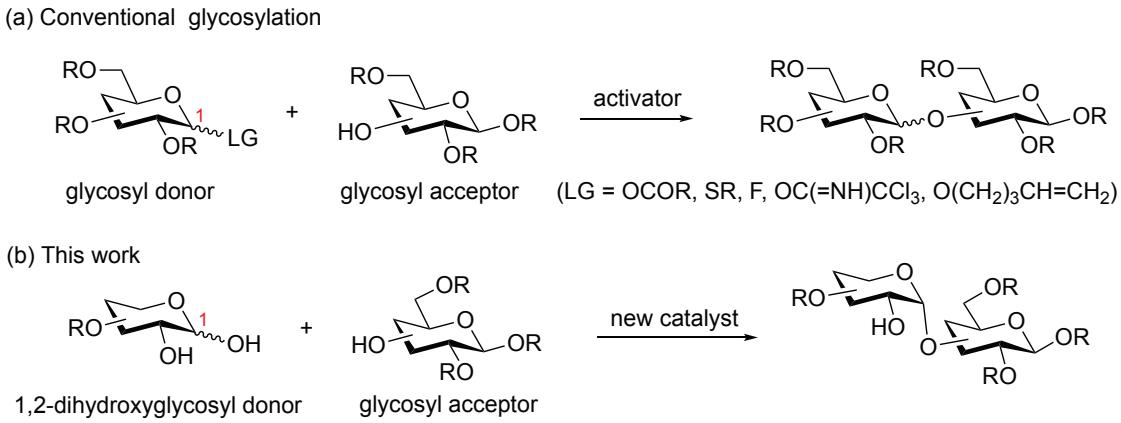
**Abstract** – We explored direct dehydrative coupling of tetrahydro-2*H*-pyran-2,3-diol or a 1,2-dihydroxy sugar with various alcohols using a range of arylboronic acids. Among the catalysts, 2-borono-4-trifluoromethylbenzoic acid efficiently promoted acetalization of tetrahydro-2*H*-pyran-2,3-diol. Ferroceniumboronic acid showed the best catalytic activity for glycosylation of the 1,2-dihydroxy sugar. The major products were 1,2-*cis*-α-D-glucopyranosides.

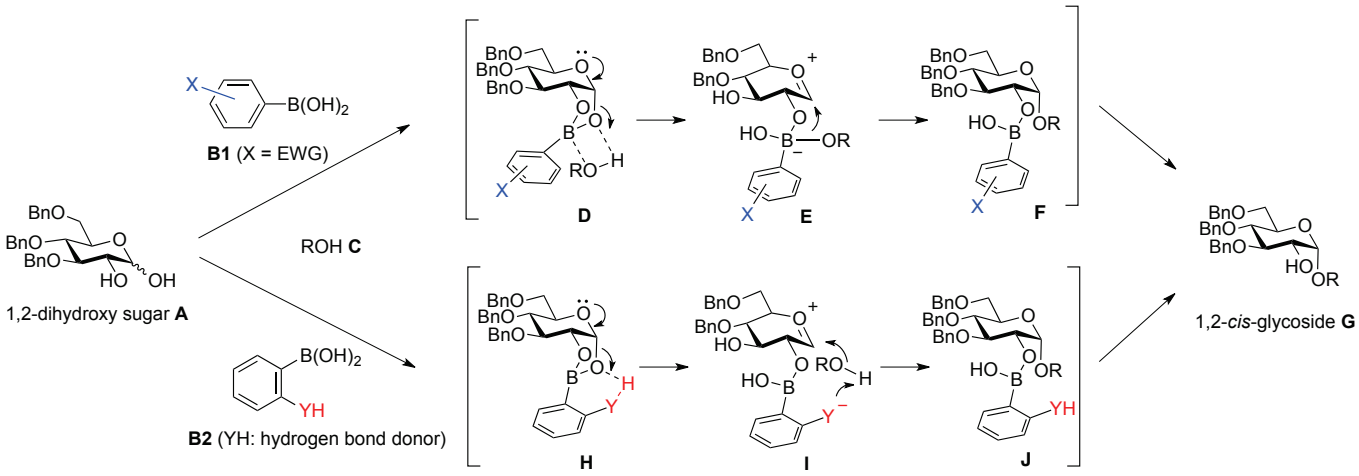
## INTRODUCTION

Glycosylation is a key step for the synthesis of oligosaccharides and glycopeptides with a range of biological activities.[1] Although there have been many reports on the glycosidic bond-forming reaction, new efficient synthetic methods remain to be explored from the perspectives of atom-economy, sustainability, yield, and selectivity. In the conventional glycosylation, glycosyl donors with acyloxy, alkylthio, halogen, 2,2,2-trichloro-1-iminoethoxy, and pent-4-enyloxy groups at the anomeric position are required for coupling with a free hydroxy group of a glycosyl acceptor in the presence of an appropriate Brønsted acid or Lewis acid (Scheme 1a).[2] The activated glycosyl donors are generally not stable and need to be prepared and stored with care. Furthermore, glycosylation sometimes requires more than the stoichiometric amount of activator or additive and cooling or heating of the reaction mixture to attain a high yield and α/β-selectivity. To overcome these limitations, we planned to investigate catalytic dehydrative glycosylation of 1,2-dihydroxy sugars as inactivated glycosyl donors in the presence of arylboronic acids[3] as catalysts (Scheme 1b).




**Scheme 1.** New concept for glycosylation

To achieve this type of glycosylation (Scheme 2), we envisioned that the boronate ester **D**, generated from electron-deficient arylboronic acid **B1** (X = electron withdrawing group) and 1,2-dihydroxy sugar **A**, would form borate complex **E** via coordination of glycosyl acceptor **C**. Successive intramolecular migration of the coordinated sugar **C** ($RO^-$) to an oxocarbenium ion intermediate (**E** → **F**) and ligand exchange of **F** with diol **A** would provide the desired glycoside **G** with 1,2-*cis*-α-selectivity. Alternatively, using arylboronic acid **B2** bearing an acidic moiety (Y–H) at the *ortho*-position, the anomeric C–O bond of the obtained boronate ester **H** would cleave through activation by an intramolecular hydrogen-bonding interaction. Then, glycosyl acceptor **C** would attack the anomeric carbon of the resulting intermediate **I** from the bottom side with assistance from the conjugate base ($Y^-$). After ligand exchange of **J** with diol **A**, this would also give **G** as the predominant product.



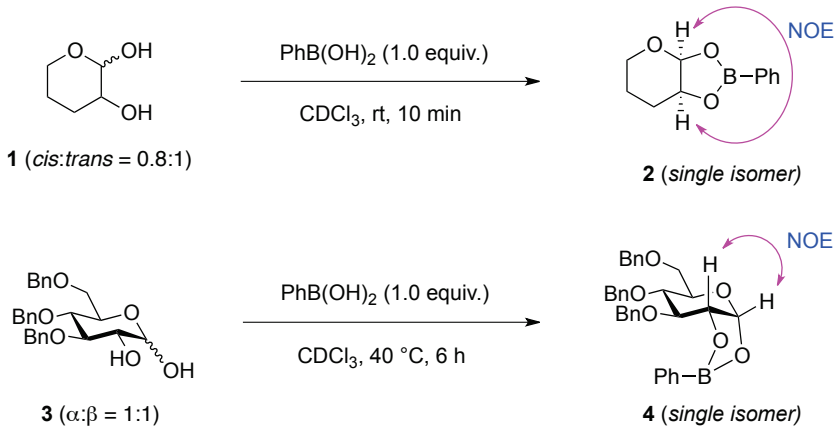

**Scheme 2.** Glycosylation of 1,2-dihydroxy sugar **A** catalyzed by arylboronic acids **B1** and **B2**

Glycosylation of 1-hydroxy sugars usually requires a stoichiometric amount of dehydrating reagent,[4] and only a few catalytic dehydrative reactions have been reported.[5,6] To date, the catalytic system

$Sn(OTf)_2/Me_3SiCl/LiClO_4$ has been identified as the best combination of catalyst and additive for α-selective glycosylation. In this paper, we describe arylboronic acid-catalyzed dehydrative coupling of a 1,2-dihydroxyglycosyl donor with several alcohols for the synthesis of 1,2-*cis*-α-D-glucopyranosides.

## RESULTS AND DISCUSSION

We first examined the reaction of phenylboronic acid and cyclic 1,2-diol (Scheme 3).[7] A 1:1 mixture of phenylboronic acid and tetrahydro-2*H*-pyran-2,3-diol **1** (*cis*:*trans* = 0.8:1) was stirred in $CDCl_3$ at room temperature for 10 min. The corresponding phenylboronate ester **2** was obtained as the only product. The same treatment of 3,4,6-tri-*O*-benzyl-D-glucopyranose **3** (α:β = 1:1) with phenylboronic acid at 40 °C for 6 h provided the *cis*-bicyclic boronate ester **4** exclusively. The configurations of **2** and **4** were determined to be cis by NOESY of the crude products. We were unable to isolate these boronates because they were not stable on silica gel.

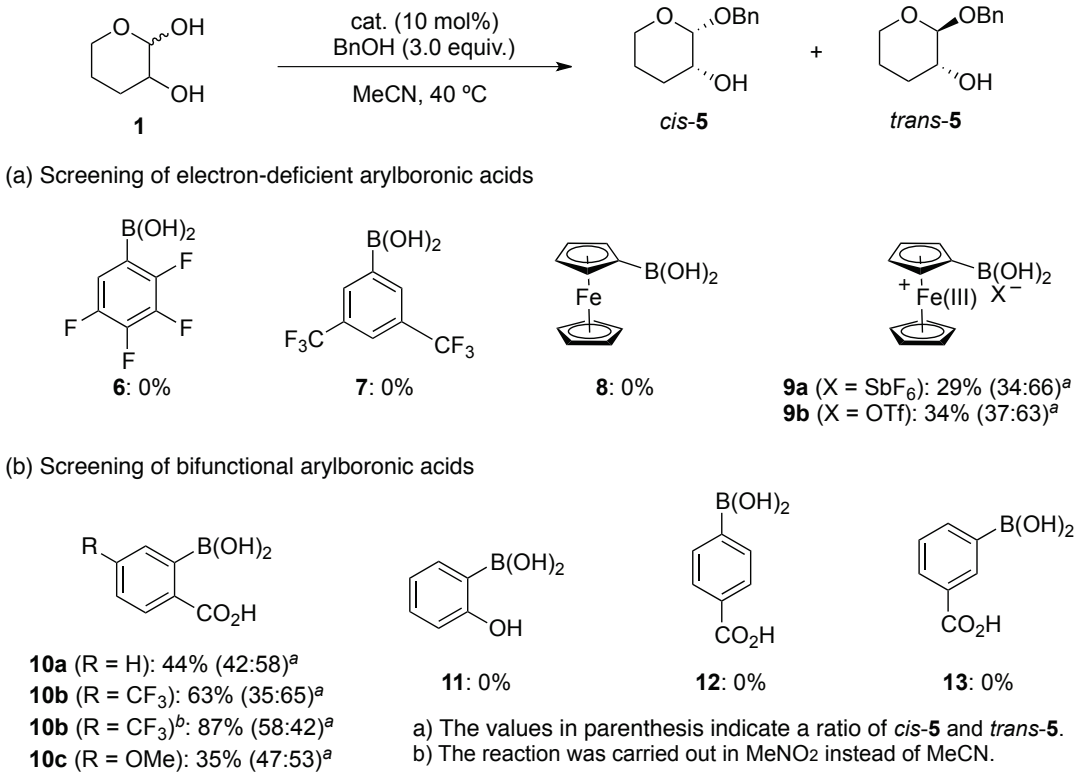



**Scheme 3.** Formation of boronate esters **2** and **4** from phenylboronic acid and 1,2-diols **1** and **3**

Having confirmed the formation of boronate ester as a reaction intermediate, we next turned our attention to acetalization of model compound **1** with benzyl alcohol in the presence of a range of arylboronic acids containing electron-deficient functional groups (Scheme 4a). Commercially available boronic acids **6–8** were inefficient for the acetalization of **1**, and did not give the desired products **5**. After screening many catalysts, we found that ferroceniumboronic acids **9a** and **9b**, which were readily prepared from ferroceneboronic acid and silver salts ($AgSbF_6$ and AgOTf),[8] showed moderate catalytic activity to produce benzyl acetals **5** in 29% (**9a**) and 34% (**9b**) yields as a mixture of C2-isomers (*cis*:*trans* = 34:66 for **9a** and 37:63 for **9b**).

Thus, we examined bifunctional arylboronic acids **10–13** to improve the yields of benzyl acetals **5** (Scheme 4b). In contrast to the result with phenol **11**, *ortho*-carboxylic acid **10a**[9] gave a better yield of **5** in a *cis*:*trans* ratio of 42:58. Moreover, use of **10b**,[9] which has a $CF_3$ group at the *para*-position, in

nitromethane dramatically improved both the yield and stereoselectivity of **5** (87%, *cis*:*trans* = 58:42) compared with the reactions of **10a** and **10b** in acetonitrile. These results suggest that the *ortho*-carboxy group plays a crucial role in the synergistic activation of the anomeric C–O bond of the presumed boronate ester **2**. This synergistic effect of boronic acid and carboxylic acid was further supported by the fact that neither dual catalysis with phenylboronic acid and benzoic acid nor use of *meta*- and *para*-substituted carboxylic acids **12** and **13** exhibited any catalytic activity.

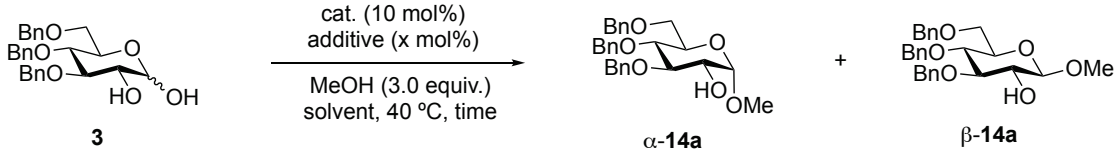



**Scheme 4.** Screening of arylboronic acids for the acetalization of **1** and BnOH

To determine what type of active arylboronic acid, **9** or **10**, was best for the acetalization, the reaction of 3,4,6-tri-*O*-benzyl-D-glucopyranose **3** with methanol in nitromethane was carried out in the presence of **9a**, **9b**, or **10b** (Table 1). Unexpectedly, the pre-prepared ferroceniumboronic acid **9a** showed the best catalytic performance, producing a 69:31 mixture of α-**14a** and β-**14a** in 78% yield (entries 1–3). By contrast, both **9b** and **10b** resulted in low yields of a mixture of α/β-**14a**. Next, we examined the reaction using ferroceniumboronic acids **9a** and **9b** prepared *in situ* from ferroceneboronic acid **8** and silver salts (entries 4 and 5). Catalysts **9a** and **9b** led to slight and significant decreases in the yield, respectively, probably because of formation of short-lived chemical species. However, the yield of **14a** improved to 82% and the reaction time decreased to 24 h when 20 mol% of $AgSbF_6$ was added to a solution of substrate **3**, pre-catalyst **8**, and methanol in nitromethane (entries 6 and 7). We evaluated the solvent

effect using 1,2-dichloroethane, ether, and THF, and found that only 1,2-dichloroethane could be used as an alternative solvent (entries 8–10).

**Table 1.** Optimization of the reaction conditions for glycosylation of **3**




**3** α-**14a** β-**14a**

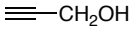
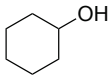
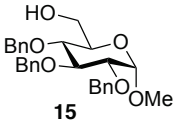
| Entry | Cat. | Additive (x mol%) | Solvent | Time (h) | Yield (%) | Ratio (α:β) |
|---|---|---|---|---|---|---|
| 1 | **9a** | | $MeNO_2$ | 48 | 78 | 69:31 |
| 2 | **9b** | | $MeNO_2$ | 48 | 12 | 59:41 |
| 3 | **10b** | | $MeNO_2$ | 48 | 9 | 53:47 |
| 4 | **8**[a] | $AgSbF_6$ (10) | $MeNO_2$ | 48 | 70 | 53:47 |
| 5 | **8**[a] | AgOTf (10) | $MeNO_2$ | 48 | trace | |
| 6 | **8**[b] | $AgSbF_6$ (10) | $MeNO_2$ | 48 | 15 | 31:69 |
| 7 | **8**[b] | $AgSbF_6$ (20) | $MeNO_2$ | 24 | 82 | 62:38 |
| 8 | **8**[b] | $AgSbF_6$ (20) | 1,2-DCE | 48 | 82 | 61:39 |
| 9 | **8**[b] | $AgSbF_6$ (20) | $Et_2O$ | 48 | 37 | 51:49 |
| 10 | **8**[b] | $AgSbF_6$ (20) | THF | 48 | 27 | 48:52 |

[a] Catalyst **9a** or **9b** was prepared *in situ* by mixing **8** and the additive in $MeNO_2$, and then adding **3** and MeOH.

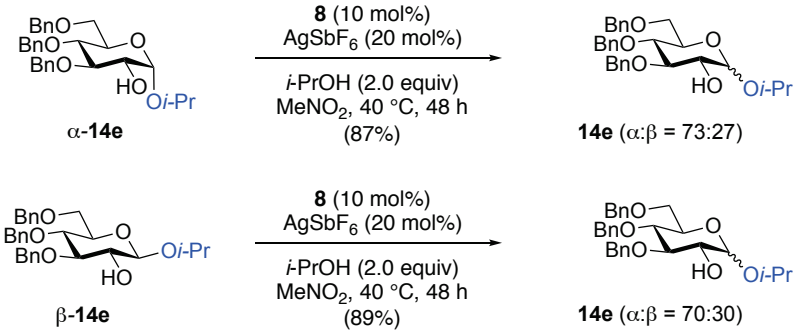
[b] Catalyst **9a** was prepared *in situ* by mixing the additive with a solution of **8**, **3**, and MeOH.

Although further enhancement of α/β-selectivity is needed, we evaluated the scope of the nucleophile under the optimized conditions. The established reaction with **3** could be applied to several primary alcohols, such as ethanol, propargyl alcohol, and 4-chlorobenzyl alcohol, to give the corresponding glucosides **14b–d** in 72%–88% yields with moderate α/β-selectivity (51:49 to 66:34) (Table 2). Secondary alcohols such as 2-propanol and cyclohexanol were also introduced into diol **3**, and gave the desired products **14e** and **14f** with good selectivities (α:β = 74:26–81:19). Notably, dehydrative glycosylation of diol **3** with methyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **15** took place smoothly under the same optimized conditions to produce 1,6-disaccharide **14g** in 52% yield as a 1:1 mixture of α- and β-isomers.

**Table 2.** Scope of the nucleophile under the optimized conditions


| Entry | ROH | Yield (α:β) |
|---|---|---|
| 1 | EtOH | **14b**: 72% (51:49) |
| 2 |  | **14c**: 79% (66:34) |
| 3 | 4-$ClC_6H_4CH_2OH$ | **14d**: 88% (61:39) |
| 4 | *i*-PrOH | **14e**: 74% (81:19) |
| 5 |  | **14f**: 58% (74:26) |
| 6 |  **15** | **14g**: 52% (50:50) |

Although we obtained the corresponding glycosides **14a–g** in reasonable yields, the α/β-selectivity was highly dependent on the alcohols used. To clarify the stereodetermining factor of the glycosylation, epimerization experiment of α-**14e** and β-**14e** was carried out under the optimized conditions (Scheme 5). To our surprise, the same treatment of α-**14e** or β-**14e** with ferroceneboronic acid **8** and $AgSbF_6$ in the presence of 2 equiv of 2-propanol resulted in a mixture of α-**14e** and β-**14e** in a similar ratio. These results suggest that the two products, α-**14** and β-**14**, are interconvertible under the conditions and that the α:β ratio is controlled thermodynamically. We suspect that any acidic species might be generated in the reaction mixture by the reaction of ferroceneboronic acid **8** and the silver salt.




**Scheme 5.** Epimerization experiment of α-**14e** and β-**14e**

In conclusion, we developed a new catalytic method for dehydrative acetalization of tetrahydro-2*H*-pyran-2,3-diol using highly electron-deficient boronic acid **9a** and bifunctional arylboronic acid **10b**. In addition, *in situ* generation of ferroceniumboronic acid **9a** gave the best catalysis for dehydrative glycosylation. Catalytic dehydrative coupling of diol donor **3** and glucoside **15** was successfully applied to the synthesis of 1,6-linked disaccharide **14g**, while both the yield and

α/β-selectivity need to be improved. Further synthetic and mechanistic studies are underway in our laboratory.

## EXPERIMENTAL

Unless otherwise noted, all chemicals and solvents were obtained from commercial suppliers and used without further purification. Analytical thin-layer chromatography was performed with Merck Silica gel 60. Column chromatography was performed on Cica silica gel 60 (spherical/40–100 μm). Proton nuclear magnetic resonance ($^1$H NMR) spectra were recorded with a JEOL JNM-AL 400 at 400 MHz, JEOL JNM-ECA 500 at 500 MHz, or Avance I 600 (Bruker Biospin AG, Switzerland) at 600 MHz. Chemical shifts are reported relative to TMS (δ 0.00) or $CD_3OD$ (δ 3.30). Multiplicity is indicated by one or more of the following: s (singlet); d (doublet); dd (doublet of doublets); t (triplet); q (quartet); m (multiplet); br (broad). Carbon nuclear magnetic resonance ($^{13}$C NMR) spectra were recorded with a JEOL JNM-AL 400 at 100 MHz, JEOL JNM-ECA 500 at 125 MHz, or Avance I 600 (Bruker Biospin AG, Switzerland) at 150 MHz. Chemical shifts are reported relative to $CDCl_3$ (δ 77.0) or $CD_3OD$ (δ 49.0). Infrared spectra were recorded on a JASCO FT/IR-4100. High resolution mass spectra were obtained on a Shimadzu LCMS-IT-TOF for ESI-MS. Optical rotations were recorded on a JASCO P-2200 polarimeter; concentrations are quoted in grams per 100 mL. Unless otherwise noted, all materials and solvents were purchased from Tokyo Kasei Co., Aldrich Inc., and other commercial suppliers and were used without purification.

### Preparation of starting materials

Compounds **1**[10] and **3**[10] are known compounds.

**Tetrahydro-2*H*-pyran-2,3-diol (1):** To a solution of *m*CPBA (15 mmol, 3.45 g) in $Et_2O$ (50 mL) were added 3,4-dihydro-2*H*-pyran (10 mmol, 0.905 mL) and $H_2O$ (5 mL) at 0 °C under argon atmosphere. The solution was stirred at 0 °C for 19 h before concentrated. Then, the mixture containing colorless precipitates was filtered through a glass filter using cold $H_2O$. After the filtrate was coevaporated with toluene, the crude was purified by column chromatography (EtOAc) to provide **1** (861 mg, 73%, *cis*:*trans* = 0.8:1) as a colorless oil; $^1$H NMR (500 MHz, $CDCl_3$, 40:60 mixture of anomers): δ 4.92 (s, 1.0H), 4.51 (d, $J$ = 5.7 Hz, 0.6H), 4.42 (s, 0.4H), 3.97–3.90 (m, 1.0H), 3.69 (s, 0.6H), 3.55–3.40 (m, 2.2H), 2.89 (s, 0.4H), 2.10–2.07 (m, 0.6H), 1.90–1.46 (m, 3.2H); $^{13}$C NMR (125 MHz, $CDCl_3$, 40:60 mixture of anomers): δ 98.5, 93.6, 70.3, 67.7, 65.1, 62.1, 29.1, 27.6, 24.0, 22.1.

**Formation of boronic esters (2 and 4) (Scheme 3)**

The compound **1** (11.8 mg, 0.10 mmol) and phenylboronic acid (12.2 mg, 0.10 mmol) were dissolved in $CDCl_3$ (0.50 mL), respectively, and both solutions were mixed at room temperature. The resulting solution was transferred to a NMR tube for taking the following spectral data; $^1$H NMR (500 MHz, $CDCl_3$): δ 7.89 (d, *J* = 7.4 Hz, 2H), 7.52 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.41 (dd, *J* = 7.7, 7.4 Hz, 2H), 5.81 (d, *J* = 5.7 Hz, 1H), 4.57 (dt, *J* = 5.7, 3.7 Hz, 1H), 3.82 (dt, *J* = 11.7, 6.9 Hz, 1H), 3.73 (dt, *J* = 11.7, 6.6 Hz, 1H), 2.10–2.04 (m, 1H), 1.94–1.86 (m, 1H), 1.78–1.72 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 135.6, 135.0, 131.8, 127.9, 98.5, 73.5, 58.0, 22.3, 16.5.

The compound **3** (22.5 mg, 0.050 mmol) and phenylboronic acid (6.1 mg, 0.050 mmol) were dissolved in $CDCl_3$ (0.50 mL), respectively. Both solutions were mixed, and stirred at 40 °C for 6 h. The resulting solution was transferred to a NMR tube for taking the following spectral data; $^1$H NMR (500 MHz, $CDCl_3$): δ 7.77 (d, *J* = 6.9 Hz, 2H), 7.42 (t, *J* = 8.3 Hz, 1H), 7.33–7.17 (m, 15H), 7.08 (t, *J* = 3.7 Hz, 2H), 5.99 (d, *J* = 5.7 Hz, 1H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 11.5 Hz, 1H), 4.56 (d, *J* = 11.5 Hz, 1H), 4.52–4.50 (m, 2H), 4.43 (d, *J* = 12.6 Hz, 1H), 4.34 (d, *J* = 11.5 Hz, 1H), 3.84 (t, *J* = 4.3 Hz, 1H), 3.70 (d, *J* = 3.4 Hz, 2H), 3.61 (d, *J* = 2.3 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 137.9, 137.8, 135.6, 135.1, 132.0, 128.5, 128.3 (2C), 128.0, 127.9, 127.8 (2C), 127.6 (2C), 99.1, 80.3, 77.1, 74.5, 73.4, 73.0, 72.3, 70.4, 69.1.

**Preparation of arylboronic acids (9 and 10)**

Catalysts **6**, **7**, **8**, and **10a** are commercially available. The known catalysts **9a**[8] and **10b**[9] were prepared according to the reported procedure.

**Ferroceniumboronic acid trifluoromethanesulfonate salt (9b):** The title compound (107 mg, 65%) was prepared as dark green solids by a similar method as described in the literature,[8] starting from ferroceneboronic acid (100 mg, 0.435 mmol) and AgOTf (112 mg, 0.435 mmol). The $^1$H and $^{13}$C NMR spectra were not able to obtain in high quality due to the paramagnetism of iron (III). $^{19}$F NMR (376 MHz, acetone-$d_6$): δ –72.3 (br s, 3F); IR (ATR): 3399, 3112, 1656, 1418, 1225, 1164, 1025 cm$^{-1}$; HRMS (ESI) calcd for $C_{11}H_{13}O_2BFe$ $[M–OTf–H_2O+CH_3OH]^+$: 244.0355; Found: 244.0362; calcd for $C_{12}H_{15}O_2BFe$ $[M–OTf–2H_2O+2CH_3OH]^+$: 258.0512; Found: 258.0517; calcd for $CO_3F_3S$ $[M–C_{10}H_{11}O_2BFe]^-$: 148.9526; Found: 148.9530.

**2-Borono-4-methoxybenzoic acid (10c):** The title compound (139 mg, 31%) was obtained as an ivory solid according to the literature,[9] starting from *tert*-butyl 4-methoxybenzoate (469 mg, 2.2 mmol); $^1$H NMR (500 MHz, $CD_3OD$): δ 7.89 (d, *J* = 8.6 Hz, 1H), 6.95 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.91 (d, *J* = 2.3 Hz, 1H), 3.85 (s, 3H); $^{13}$C NMR (125 MHz, $CD_3OD$): δ 172.1, 164.8, 132.1, 131.2, 127.0, 116.2, 114.8, 55.9;

IR (ATR): 3201, 1596, 1463, 1286, 1242, 1148, 1086, 869 $cm^{-1}$; HRMS (ESI) calcd for $C_{10}H_{12}O_5B$ $[M-2H_2O+2CH_3OH-H]^-$: 223.0785; Found: 223.0783.

**General procedure for the synthesis of benzyl acetals (5) with arylboronic acids (6–13) (Scheme 4)**

Both *cis*-**5**[11] and *trans*-**5**[12] are known compounds, but their $^{13}C$ NMR spectral data have not been reported.

**2-(Benzyloxy)tetrahydro-2*H*-pyran-3-ol (*cis*-5 and *trans*-5):** To a mixture of **1** (0.10 mmol, 11.8 mg) and catalyst (0.010 mmol) in MeCN (1.0 mL) was added BnOH (0.30 mmol, 31 μL). The reaction mixture was stirred at 40 °C for 48 h, before concentrated. The crude was purified by column chromatography (hexane/EtOAc = 3:1) to provide a mixture of *cis*-**5** and *trans*-**5** as a colorless oil.

*cis*-**5**: $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.37–7.30 (m, 5H), 4.82 (d, *J* = 11.0 Hz, 1H), 4.81 (d, J = 2.9 Hz, 1H), 4.53 (d, *J* = 11.0 Hz, 1H), 3.73 (td, *J* = 10.4, 3.9 Hz, 1H), 3.66–3.64 (m, 1H), 3.55–3.52 (m, 1H), 2.02 (br s, 1H), 1.87–1.67 (m, 4H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 137.6, 128.4, 127.9, 127.8, 97.7, 69.2, 68.0, 59.9, 27.7, 24.1.

*trans*-**5**: $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.37–7.30 (m, 5H), 4.86 (d, *J* = 11.6 Hz, 1H), 4.55 (d, *J* = 11.6 Hz, 1H), 4.38 (d, *J* = 5.8 Hz, 1H), 3.97–3.92 (m, 1H), 3.56–3.47 (m, 2H), 2.35 (br s, 1H), 2.11–2.03 (m, 1H), 1.79–1.49 (m, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 137.5, 128.4, 128.0, 127.8, 102.3, 69.9, 68.5, 63.7, 28.0, 22.9.

**General procedure for the synthesis of methyl 3,4,6-tri-*O*-benzyl-D-glucopyranoside (14a) (Table 1)**

Both α-**14a**[13] and β-**14a**[14] are known and their spectral data were identical to the reported data of the authentic samples.

**(Method A in entries 1–3)** The reaction was performed in $MeNO_2$ according to the procedure for the synthesis of **5**, giving a mixture of α-**14a** and β-**14a**.

**(Method B in entries 4–5)** A mixture of **8** (0.010 mmol) and $AgSbF_6$ or AgOTf (0.010 mmol) in $MeNO_2$ (0.10 mL) was stirred at room temperature for 30 min under argon atmosphere. Then, MeOH (0.30 mmol) and a solution of **3** (0.10 mmol) in $MeNO_2$ (1.9 mL) were successively added, and the resulting mixture was stirred at 40 °C for 48 h. Then, the mixture was concentrated at 30–35 °C. The crude was purified by column chromatography (hexane/EtOAc = 2:1 → 1:1) to afford a mixture of α-**14a** and β-**14a**.

**(Method C in entries 6–10)** To a solution of **3** (0.10 mmol), **8** (0.010 mmol), and MeOH (0.30 mmol) in $MeNO_2$ (2.0 mL) was added $AgSbF_6$ (0.010 or 0.020 mmol) in a glove box, and the reaction mixture was stirred at 40 °C for 24 h. Then, the reaction mixture was concentrated at 30–35 °C. The crude was purified by column chromatography (hexane/EtOAc = 2:1 → 1:1) to afford a mixture of α-**14a** and β-**14a**.

**Ethyl 3,4,6-tri-*O*-benzyl-D-glucopyranoside (14b) (Entry 1 in Table 2):** The reaction was performed according to method C for the synthesis of **14a**, providing a mixture of α-**14b** and β-**14b** (34.5 mg, 72%,

α:β = 51:49), starting from substrate **3** (45.1 mg, 0.10 mmol) and EtOH (17.5 μL, 0.30 mmol). The spectral data of β-**14b** were identical to the reported data of the authentic sample.[15]

α-**14b**: A colorless solid; $[\alpha]_D^{25}$ +81.7 (*c* 1.0, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$): δ 7.39–7.27 (m, 13H), 7.14 (dd, *J* = 7.7, 2.2 Hz, 2H), 4.94 (d, *J* = 11.0 Hz, 1H), 4.91 (d, *J* = 3.8 Hz, 1H), 4.85 (d, *J* = 11.0 Hz, 1H), 4.82 (d, *J* = 11.0 Hz, 1H), 4.63 (d, *J* = 12.1 Hz, 1H), 4.51 (d, *J* = 12.1 Hz, 1H), 4.49 (d, *J* = 10.4 Hz, 1H), 3.80–3.74 (m, 4H), 3.71 (dd, *J* = 9.3, 3.8 Hz, 1H), 3.67 (dd, *J* = 10.7, 1.9 Hz, 1H), 3.64 (t, *J* = 9.3 Hz, 1H), 3.54 (dq, *J* = 9.3, 7.1 Hz, 1H), 2.12 (br s, 1H), 1.23 (t, *J* = 7.1 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): δ 138.7, 138.2, 137.9, 128.4 (2C), 127.9 (3C), 127.7 (2C), 127.6, 98.1, 83.5, 77.4, 75.3, 75.0, 73.5, 73.0, 70.5, 68.5, 63.5, 15.0; IR (ATR): 3455, 3030, 2911, 1453, 1361, 1273, 1043, 1027 $cm^{-1}$; HRMS (ESI) calcd for $C_{29}H_{34}O_6Na$ $[M+Na]^+$: 501.2248; Found: 501.2237.

**Propargyl 3,4,6-tri-*O*-benzyl-D-glucopyranoside (14c) (Entry 2 in Table 2):** The reaction was performed according to method C for the synthesis of **14a**, providing a mixture of α-**14c** and β-**14c** (38.4 mg, 79%, α:β = 66:34), starting from substrate **3** (45.1 mg, 0.10 mmol) and $HC{\equiv}CCH_2OH$ (17.7 μL, 0.30 mmol). The spectral data of β-**14c** were identical to the reported data of the authentic sample.[16]

α-**14c**: A colorless oil; $[\alpha]_D^{25}$ +92.8 (*c* 0.50, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.38–7.27 (m, 13H), 7.15 (dd, *J* = 7.2, 2.0 Hz, 2H), 5.10 (d, *J* = 2.9 Hz, 1H), 4.92 (d, *J* = 11.5 Hz, 1H), 4.85 (d, *J* = 11.5 Hz, 1H), 4.82 (d, *J* = 10.9 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.50 (d, *J* = 10.9 Hz, 1H), 4.28 (d, *J* = 2.3 Hz, 2H), 3.82–3.74 (m, 4H), 3.68–3.64 (m, 2H), 2.44 (t, *J* = 2.3 Hz, 1H), 2.12 (d, *J* = 8.0 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 138.6, 138.1, 137.8, 128.4 (3C), 127.9 (2C), 127.7 (2C), 97.2, 83.1, 78.6, 77.2, 75.4, 75.0 (2C), 73.5, 72.7, 71.1, 68.3, 54.8; IR (ATR): 3546, 3286, 3030, 2922, 2863, 1496, 1454, 1360, 1039 $cm^{-1}$; HRMS (ESI) calcd for $C_{30}H_{32}O_6Na$ $[M+Na]^+$: 511.2091; Found: 511.2084.

**4-Chlorobenzyl 3,4,6-tri-*O*-benzyl-D-glucopyranoside (14d) (Entry 3 in Table 2):** The reaction was performed according to method C for the synthesis of **14a**, providing a mixture of α-**14d** and β-**14d** (50.6 mg, 88%, α:β = 61:39), starting from substrate **3** (45.1 mg, 0.10 mmol) and 4-$ClC_6H_4CH_2OH$ (42.8 mg, 0.30 mmol).

α-**14d**: A colorless oil; $[\alpha]_D^{25}$ +64.0 (*c* 0.86, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$): δ 7.37–7.27 (m, 17H), 7.14 (dd, *J* = 7.4, 1.9 Hz, 2H), 5.00 (d, *J* = 3.8 Hz, 1H), 4.91 (d, *J* = 11.0 Hz, 1H), 4.84 (d, *J* = 11.0 Hz, 1H), 4.81 (d, *J* = 11.0 Hz, 1H), 4.70 (d, *J* = 12.1 Hz, 1H), 4.62 (d, *J* = 12.1 Hz, 1H), 4.52 (d, *J* = 12.1 Hz, 1H), 4.51 (d, *J* = 12.1 Hz, 1H), 4.49 (d, *J* = 12.1 Hz, 1H), 3.80–3.71 (m, 4H), 3.64 (dd, *J* = 9.9, 8.8 Hz, 1H), 3.61 (dd, *J* = 10.7, 1.9 Hz, 1H), 2.09 (d, *J* = 8.8 Hz, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): δ 138.6, 138.0, 137.9, 135.5, 133.8, 129.5, 128.7, 128.4 (2C), 128.2, 127.9 (3C), 127.8, 127.7 (2C), 97.9, 83.3,

77.4, 75.4, 75.1, 73.5, 72.9, 70.9, 69.0, 68.4; IR (ATR): 3446, 3031, 2922, 1492, 1453, 1027, 1013 $cm^{-1}$; HRMS (ESI) calcd for $C_{34}H_{35}O_6ClNa$ $[M+Na]^+$: 597.2014; Found: 597.2012.

β-**14d**: A colorless solid; $[\alpha]_D^{25}$ −16.4 (*c* 1.1, $CHCl_3$); $^1H$ NMR (600 MHz, $CDCl_3$): δ 7.37–7.27 (m, 17H), 7.18 (d, *J* = 7.7 Hz, 2H), 4.90 (d, *J* = 11.5 Hz, 1H), 4.89 (d, *J* = 12.1 Hz, 1H), 4.83 (d, *J* = 11.5 Hz, 2H), 4.62 (d, *J* = 12.1 Hz, 1H), 4.60 (d, *J* = 11.5 Hz, 1H), 4.54 (d, *J* = 12.1 Hz, 2H), 4.34 (d, *J* = 7.1 Hz, 1H), 3.75 (d, *J* = 11.0 Hz, 1H), 3.70 (dd, *J* = 11.0, 4.4 Hz, 1H), 3.64–3.56 (m, 3H), 3.48 (dd, *J* = 9.9, 4.4 Hz, 1H), 2.32 (br s, 1H); $^{13}C$ NMR (150 MHz, $CDCl_3$): δ 138.5, 138.1, 138.0, 135.7, 133.7, 129.4, 128.6, 128.5, 128.4 (2C), 127.9 (2C), 127.8 (2C), 127.7 (2C), 101.7, 84.5, 77.5, 75.2 (2C), 75.0, 74.6, 73.5, 70.2, 68.8; IR (ATR): 3288, 3030, 2923, 1494, 1451, 1361, 1059, 1043 $cm^{-1}$; HRMS (ESI) calcd for $C_{34}H_{35}O_6ClNa$ $[M+Na]^+$: 597.2014; Found: 597.2010.

**Isopropyl 3,4,6-tri-*O*-benzyl-D-glucopyranoside (14e) (Entry 4 in Table 2):** The reaction was performed according to method C for the synthesis of **14a**, providing a mixture of α-**14e** and β-**14e** (36.5 mg, 74%, α:β = 81:19), starting from substrate **3** (45.1 mg, 0.10 mmol) and *i*-PrOH (23.0 μL, 0.30 mmol). The spectral data of the obtained products α-**14e** and β-**14e** were identical to the reported data of the authentic samples α-**14e**[17] and β-**14e**.[14,17]

**Cyclohexyl 3,4,6-tri-*O*-benzyl-D-glucopyranoside (14f) (Entry 5 in Table 2):** The reaction was performed according to method C for the synthesis of **14a**, providing a mixture of α-**14f** and β-**14f** (30.8 mg, 58%, α:β = 74:26), starting from substrate **3** (45.1 mg, 0.10 mmol) and $C_6H_{11}OH$ (31.7 μL, 0.30 mmol). The spectral data of the obtained products α-**14f** and β-**14f** were identical to the reported data of the authentic samples α-**14f**[13] and β-**14f**.[14]

**Methyl 3,4,6-tri-*O*-benzyl-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (14g) (Entry 6 in Table 2):** The reaction was performed according to method C for the synthesis of **14a**, providing a mixture of α-**14g** and β-**14g** (46.6 mg, 52%, α:β = 50:50), starting from substrate **3** (45.1 mg, 0.10 mmol) and **15** (139 mg, 0.30 mmol). The spectral data of the obtained products α-**14g** and β-**14g** were identical to the reported data of the authentic samples α-**14g** and β-**14g**.[18]

**The epimerization experiment of α-14e and β-14e (Scheme 5):** To a solution of α-**14e** (24.6 mg, 50 μmol), **8** (1.1 mg, 5.0 μmol), and *i*-PrOH (7.7 μL, 0.10 mmol) in $MeNO_2$ (1.0 mL) was added $AgSbF_6$ (3.4 mg, 10 μmol) in a glove box, and the reaction mixture was stirred at 40 °C for 48 h. Then, the reaction mixture was concentrated at 30–35 °C. The crude was purified by column chromatography (hexane/EtOAc = 3:1) to give a mixture of α-**14e** and β-**14e** (21.5 mg, 87%, α:β = 73:27).

The reaction of β-**14e** (23.2 mg, 47 μmol) was performed in the same way, providing a mixture of α-**14e** and β-**14e** (20.7 mg, 89%, α:β = 70:30).

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